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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,807	PORT ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-20* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/05, 9/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 10/09/2009 is acknowledged. The election with traverse of the following species is also acknowledged: Gly-Pro-D-Leu-D-Ala as peptide and iron oxide as signal.

The traversal is on the ground(s) that the Unity of Invention Requirement is respectfully traversed as it is submitted that the Administrative Instructions under the PCT allows Applicant at least one additional method-of-use claim category embodiment with the present elected product. See MPEP, Annex B, Unity of Invention, Section (e), pages AI-58 to AI59 (Rev. 6, Sept. 2007). In the present situation, at least Group II should be examined with elected Group I. Also, it is submitted that all of the present claims share the special technical feature of the diagnostic agent of claim 1 containing the peptide (a). Finally, it is submitted that there is no undue burden placed on the Examiner to additionally examine the subject matter of Groups III-V which are methods of use of the elected product subject matter that overlaps with the subject matter of Group II.

This is not found to be persuasive. In response to Applicant's response that the all of the claims share the special technical feature of elected Group I, it is noted that an international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept

(PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature", should be considered with respect to novelty and inventive step.

The common technical feature in all the groups is a diagnostic agent of formula (1). This element cannot be a special technical feature under PCT Rule 13.2 because the element is shown in the prior art.

US 2004/0018561 teaches compounds comprising peptide sequence Pro-Leu-Ala conjugated to a fluorescent moiety via linker (see claim 7). As a result, no special technical features exist among the different groups because the invention in Group 1, claim 1, fails to make a contribution over the prior art with respect to novelty or inventive step. In conclusion, there is lack of unity of inventions in the amended claims, and therefore restriction for examination purposes as indicated is proper. With respect to the argument that a method of use should be included, it is noted that claims 12 and 13 in Group 1 are method claims. With respect to the argument that searching all Groups

would not require undue burden because of overlapping subject matter, search burden can be shown for example if the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); the prior art applicable to one invention would not likely be applicable to another invention; the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. In the instant case, at least different search strategies would be necessary to search each of the different diseases and conditions listed in claims 14-20.

Status of Claims

Claims 1, 3, 5-7, 14, 15, 18 and 20 have been amended. Claims 1-9 and 12-20 are pending of which claims 5-7 are withdrawn from consideration at this time as being drawn to non-elected species. Claims 14-20 are withdrawn as being drawn to a non-elected invention. Claims 1-4, 8, 9, 12 and 13 are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 8, 9, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a diagnostic

agent comprising a compound of formula (I) (PEPTIDE)n1 - (LINKER)n2 – (SIGNAL)n3. However, the claims are devoid of a definition of variables n1, n2 and n3, therefore the claims are unclear regarding the identity of the claimed diagnostic agent. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claims 1-4, 8, 9, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a diagnostic agent comprising a compound of formula (I) (PEPTIDE)n1 - (LINKER)n2 – (SIGNAL)n3. In line 18 of the independent claim, with regard to LINKER, it is recited that "LINKER eventually absent represents a chemical link between PEPTIDE and SIGNAL." Such language is confusing because it is unclear whether LINKER is present or absent?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter (US 6,656,448) in view of Odake (US 5,100,874).

Carpenter discloses MRI contrast agents comprising one or more matrix metalloproteinase inhibiting targeting moieties attached to one or more paramagnetic metal ions, further comprising an optional linking moiety, L_n, between the targeting moieties and the paramagnetic metal ions. The paramagnetic metal ions are present in the form of metal complexes or metal oxide particles (column 45, lines 24+). Iron is described as suitable paramagnetic metal. The pharmaceuticals have the formulae, $(Q)_d$--L_n—(C_h--X), $(Q)_d$--L_n --(C_h-X_1)$_{d'}$, **$(Q)_d$--L_n--(X_2)$_{d''}$,** and $(Q)_d$--L_n--(X_3), wherein Q represents a compound that inhibits a matrix metalloproteinase, d is 1-10, d'=1-100, L_n represents an optional linking group, C_h represents a metal chelator or bonding moiety, X represents a radioisotope, X_1 represents paramagnetic metal ion, X_2 represents a paramagnetic metal ion or heavy atom containing insoluble solid particle, d" is 1-100, and X_3 represents a surfactant microsphere of an echogenic gas (column 46, lines 1-28). Suitable MMP inhibitors include peptides, etc. (column 46). With regard to the targeting ligand, a functional group, such as --CONH--, OH, --COOH, or --SH, is necessary for a molecule to be an effective inhibitor of MMPs. This functional group is involved in the chelation of the active site zinc ion, and is commonly referred to as the zinc binding group or ZBG. The hydroxamate, for example, is a bidentate ligand for

zinc (column 46, lines 10-20). See also column 46-50, including succinyl hydroxamates and alanine hydroxamates as inhibitors. There are three key features of the pharmaceuticals that determine their efficacy: MMP selectivity, inhibitory potency, typically expressed as the K_i value, and the rate of clearance from the blood. Preferred pharmaceuticals of the present invention are comprised of inhibitors, Q, which exhibit selectivity for MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14 alone or in combination over the other MMPs. Most preferred are comprised of inhibitors, Q, which exhibit selectivity for MMP-2, MMP-9, or MMP-14 alone or in combination over the other MMPs. K_i values for the preferred pharmaceuticals of the present invention are <100 nM for one or more of MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14. K_i values for the most preferred pharmaceuticals of the present invention are <10 nM for one or more of MMP-2, MMP-9, or MMP-14.

A number of methods can be used to attach the MMP inhibitors, Q, to paramagnetic metal ion or heavy atom containing solid particles,X_2, by one of skill in the art of the surface modification of solid particles. In general, the targeting moiety Q or the combination $(Q)_d L_n$ is attached to a coupling group that react with a constituent of the surface of the solid particle. The coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

The imaging agents targeted to one or more MMP's would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes. These imaging agents,

containing a ligand directed at one or more MMP's (e.g. MMP-1, MMP-2, MMP-3, MMP-9), will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases (column 3, lines 51+).

Carpenter does not specifically recite that hydroxamic tetrapeptide derivatives, such as p-aminobenzoy-Gly-Pro-D-Leu-Dala-NHOH is used as the MMP targeting ligand.

Okane discloses peptide derivatives having specific inhibitory activity against collagenases (abstract). Abnormal overaction of collagenases is shown in processes of destruction and repair of tissues, and is observed for example in cases such as rheumatoid arthritis, periodontal diseases, etc. Inhibition of collagenases provides a useful means for treating such diseases (column 1, lines 1-22). New peptide compounds which selectively inhibit the action of collagenases derived from vertebrates without inhibiting other protease actions (i.e. exhibit an inhibitory action of high specificity), and which have low toxicity, improved metabolic rate are disclosed, including peptidylhydroxamic acid derivatives of general formula X^1-X^2-X^3-X^4-NHOH (column 1, lines 45+). In particular, p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH is disclosed (claim 6). See also claim 1. Inhibitory activity against collagenases is disclosed in Tables 1 and 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ the hydroxamic acid tetrapeptide derivatives of Okane as MMP inhibitor (Q) in the compounds and methods of Carpenter, such as $(Q)_d$--L_n--$(X_2)_{d"}$, wherein Q represents a compound that inhibits a matrix metalloproteinase, L_n

represents an optional linking group, and X_2 represents a paramagnetic metal ion containing insoluble solid particle (iron oxide). For example, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the hydroxamic acid tetrapeptide derivatives, such as aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH as functional equivalent to succinyl hydroxamates and alanine hydroxamates as inhibitors disclosed by Carpenter. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components and their functions were known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known MMP (collagenase) inhibitor for another, and the results of the substitution would have been predictable, that is effective conjugation of the MMP inhibitor to a diagnostic moiety for targeting MMP in localized imaging methods.

Claims 1-4, 8, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter (US 6,656,448) in view of Odake (US 5,100,874), further in view of Portet (*J. Colloid Interfac. Sci.*, 2001, 238, p. 37-42).

The rejection over Carpenter in view of Odake is applied as above. It would have been further obvious to provide bis-phosphonate coating on iron oxide particles used as diagnostic moiety when the teachings of Carpenter and Odake are taken in view of Portet.

Portet discloses iron oxide nanoparticles as contrast agents in magnetic resonance imaging. Bisphosphonate coating on iron oxide provided the most stable coating in a wide range of pH, including neutrality, in comparison to carboxylates, sulfonates, etc.(abstract, page 42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide iron oxide particles coated with gem-bisphosphonate as the diagnostic moiety (paramagnetic metal ion oxide particle) in the compositions of Carpenter for use in targeted MRI imaging of MMP (collagenase) activity. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Portet teaches that bisphosphonate coated iron oxide particles are efficiently stabilized (page 42). In addition, Carpenter teaches that in synthesis, the coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS